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Case Report

Severe cytomegalovirus colitis with hemolytic anemia mimicking travelers' diarrhea

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SUMMARY

A case of cytomegalovirus (CMV) colitis mimicking travelers' diarrhea following short-term travel is reported. The patient was a Croatian man visiting Korea for work. He presented with fever and severe bloody diarrhea. He was diagnosed with a primary CMV infection complicated with CMV colitis and hemolytic anemia and recovered with antiviral therapy and concomitant steroid therapy.

1. Introduction

Cytomegalovirus (CMV) colitis is a common presentation of CMV disease in immunocompromised hosts, including those with AIDS, a hematological malignancy, or on steroid therapy. The major clinical manifestations are fever, diarrhea, gastrointestinal bleeding, and abdominal pain. Although CMV colitis has been reported in immunocompetent patients, it is not commonly considered in healthy travelers with acute diarrhea.[1] A case of CMV colitis with hemolytic anemia in an immunocompetent traveler, a Croatian man who had recently arrived in Korea, is reported.

2. Case report

A 31-year-old Croatian man, without any relevant past medical history, was admitted to hospital after 7 days of fever and watery and bloody diarrhea. The patient lived in Zagreb, Croatia, and had come to Geoje Island in the southeastern area of South Korea via Istanbul, Turkey, for work as an electrician. The day after he arrived in Korea, he began to have watery diarrhea over 10 times per day (day 1 of illness); on day 3 of illness, he was admitted to a hospital in Geoje Island. At the time of admission, travelers' diarrhea due to a bacterial infection was suspected, and he was treated with cefolatam and metronidazole. Because the diarrhea continued, the antibiotics were changed to ciprofloxacin and metronidazole; however the diarrhea and fever persisted. The patient's temperature was over 38 °C during this 7-day hospital stay. On day 7 of his illness, the patient was transferred to the Infectious Disease Clinic at Pusan National University Hospital.

On admission (hospital day 1), his body temperature was 38.6 °C, blood pressure was 122/69 mmHg, and heart rate was 87 beats per min. The patient had watery and bloody diarrhea more than 10 times a day. Physical examination revealed minimal tenderness in the left lower abdomen without rebound. Laboratory tests showed a white blood cell count of 6.3×10^9 cells/l, hemoglobin 14.37 g/dl, and elevated levels of aspartate aminotransferase (AST) 70 IU/l, alanine aminotransferase (ALT) 70 IU/l, and lactate dehydrogenase (LDH) 1010 IU/l (normal range 135–225 IU/l). Bilirubin levels were normal. Serological tests for hepatitis A, B, and C and HIV were all negative. Stool cultures for Salmonella and Shigella were negative, and *Clostridium difficile* toxin was not detected in stool. PCR for astrovirus, rotavirus, adenovirus, and norovirus was negative, and PCR for Vibrio, Salmonella, Shigella, Campylobacter, Yersinia, and Enterococcus was negative. Examination for parasite eggs and protozoa was negative.

A peripheral blood smear at the time of admission showed numerous atypical lymphocytes. Epstein–Barr virus anti-viral

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capsid antigen (EBV anti-VCA) IgM was negative and EBV nuclear antigen (EBNA) IgG was positive. The results for CMV infection were as follows: CMV IgM positive, CMV IgG negative, CMV antigenemia 80/2 × 10^6 granulocytes, and CMV real-time PCR of blood 94.5 copies/μl using an Artus CMV RGQ MDx kit (Qiagen, Hilden, Germany). Computed tomography scans showed whole colon wall thickening with fat strands. Sigmoidoscopy revealed continuous lesions with edema and losses of vascularity in the rectum and sigmoid colon (Figure 1). Hematoxylin–eosin (HE) stain of a mucosal biopsy specimen showed acute inflammation and enlarged cells with inclusion bodies (Figure 2A, B). Immunohistochemical staining of the colon tissue for a CMV antigen showed numerous positive cells for CMV (Figure 2C) (monoclonal mouse anti-cytomegalovirus, clone CCH2 DDG9; Dako, Glostrup, Denmark). In addition, qualitative CMV PCR was positive in the biopsy tissue.

The patient was treated with ganciclovir (5 mg/kg twice a day) on hospital day 6. On hospital day 10, CMV antigenemia had decreased to 1/2 × 10^6 granulocytes. However, fever and fatigue persisted, and the anemia and elevated LDH had not normalized. After 5 days of ganciclovir therapy (hospital day 11), hemoglobin decreased by 8.0 g/dl. LDH was 733 IU/l and haptoglobin was 27 mg/dl (normal range 30–200 mg/dl). Direct and indirect Coombs tests were negative.

Because of persistent fever and hemolytic anemia, intravenous methylprednisolone 1 mg/kg/day was started. After the initiation of steroid therapy, the patient's fever and general condition improved. The patient was discharged in a good condition with valganciclovir 900 mg per day and tapering prednisolone for 6 days.

3. Discussion

Travelers' diarrhea usually occurs in the first week of travel. It can be caused by bacterial, viral, and parasitic organisms, and bacterial agents are the most common cause of acute diarrhea. Enterotoxigenic *Escherichia coli* represents the most common etiology, followed by Shigella and Salmonella.[2] At first, infectious diarrhea caused by bacteria was suspected and the patient was treated with antibiotics. Despite the antibiotic therapy, the severe bloody diarrhea and fever worsened. Numerous atypical lymphocytes seen on peripheral blood smear and splenomegaly were the clues for primary infection with CMV colitis.

The seroprevalence of CMV infection varies across regions. In European countries, the seroprevalence ranges between 30% and 88%.[3] However, CMV seroprevalence in pregnant women in Korea has been reported to be 98.1%,[4] which is much higher than in Western countries. It was difficult to assume CMV infection in the present case.

CMV can cause asymptomatic infection or infectious mononucleosis in immunocompetent patients. However, CMV colitis may develop in immunocompetent patients in some condition. A recent report by Rinaldo et al. showed that CMV colitis was diagnosed in

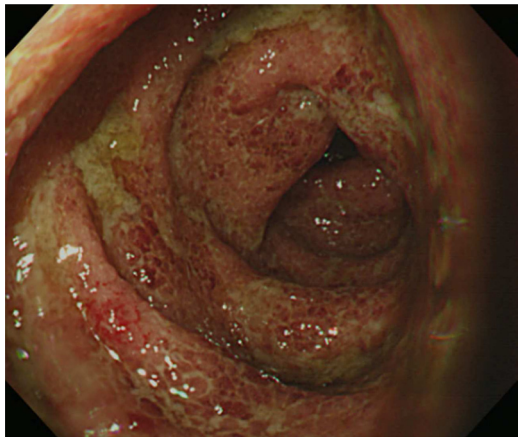

Figure 1. Endoscopic examination of the rectum and the sigmoid colon showing continuous swelling and ulcerative lesions of the mucosa, with exudates and loss of vascularity.

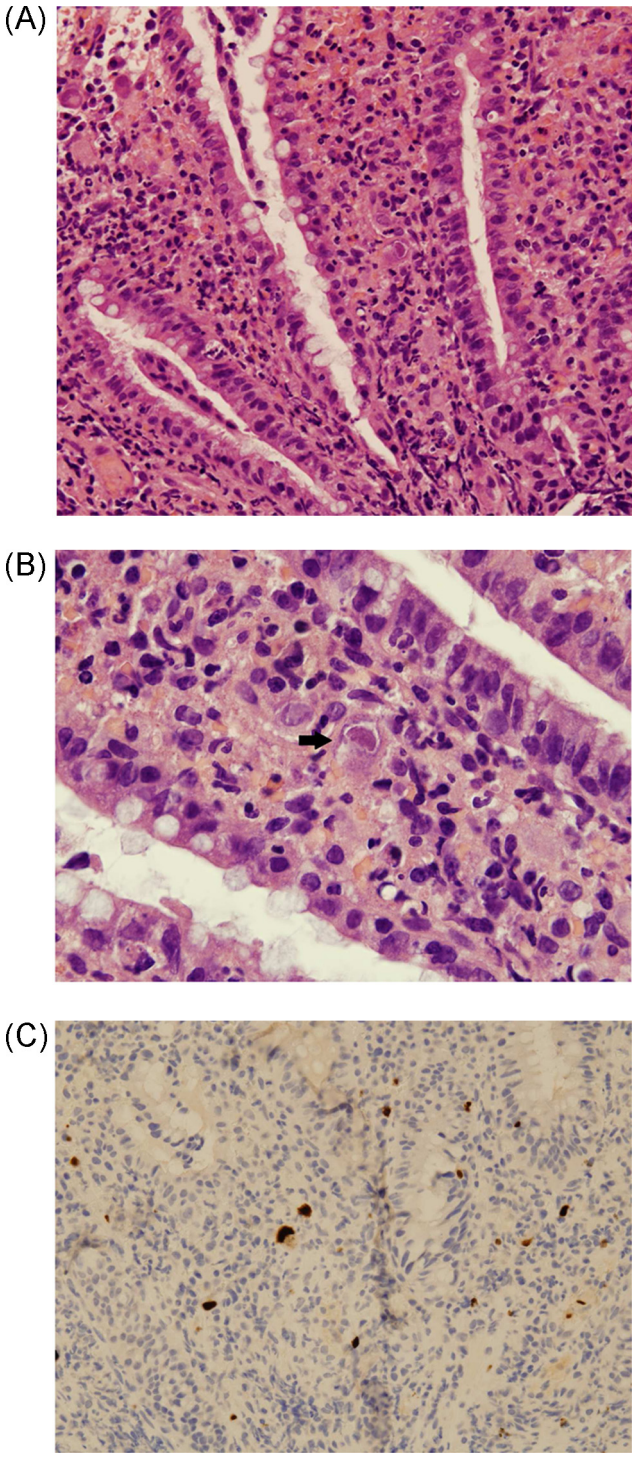

Figure 2. Biopsies of the colonic mucosa. (A) Some atypical large mesenchymal cells with a large basophilic intranuclear inclusion (Cowdry type A inclusion) are present in the lamina propria of the inflamed colonic mucosa (HE, ×400). (B) A large stromal cell with distinctive intranuclear inclusion surrounded by a clear halo (arrow; HE, ×1000). (C) Several scattered stromal cells showing positive immunoreactivity to CMV antibody in the nuclei of stromal cells (×400).

14 immunocompetent patients, all of them with comorbidities such as congestive heart failure, chronic kidney disease, and diabetes mellitus. Active CMV infection occurs frequently in intensive care unit patients. Critically ill patients undergo a transient decline of the immune system, predisposing them to CMV reactivations.[5] Clinical manifestations of CMV colitis are abdominal pain, fever, and diarrhea, and are similar to those of other infectious diarrhea. However, hematochezia or melena is frequently reported.[1] Therefore, a high suspicion is important in patients with different clinical manifestations, and early diagnosis and appropriate treatment are essential.

The outcome of CMV colitis is generally favorable. There is no current consensus on antiviral therapy for CMV colitis in immunocompetent patients.[1] In the case presented here, the patient was treated with ganciclovir because he had severe colitis and a persistent fever despite supportive care.

Hemolytic anemia is a rare complication of CMV infection in the immunocompetent host. The pathogenesis of hemolysis secondary to CMV infection is unclear, but may involve an autoimmune mechanism, with cross-reactivity to CMV and human erythrocytes and abnormal immunological activation occurring during CMV infection.[6] No evidence of an autoimmune mechanism of hemolytic anemia was identified in the patient presented here; however, because the fever and anemia persisted, steroid therapy with a concomitant antiviral agent was tried, and the fever and hemolytic anemia improved significantly.

In summary, we have reported a case of primary CMV infection complicated with colitis and hemolytic anemia in a Croatian traveler who had recently arrived in Korea. The patient recovered after treatment with ganciclovir and steroids. Clinicians should be aware of CMV colitis in cases of travelers' diarrhea with persistent bloody diarrhea and fever despite the use of empirical antibiotics.

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